

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
15 April 2004 (15.04.2004)

PCT

(10) International Publication Number
WO 2004/031109 A3

(51) International Patent Classification⁷: **C07C 29/40**,
29/36, 29/38, C07F 9/28

(21) International Application Number:
PCT/EP2003/010568

(22) International Filing Date:
23 September 2003 (23.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02405847.1 1 October 2002 (01.10.2002) EP

(71) Applicant (for all designated States except US): **CIBA
SPECIALTY CHEMICALS HOLDING INC.** [CH/CH];
Klybeckstrasse 141, 4057 Basel (CH).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **BERENS, Ulrich**
[DE/DE]; Im Unterwörth 38A, 79589 Binzen (DE).

(74) Common Representative: **CIBA SPECIALTY CHEMI-
CALS HOLDING INC.**; Patentabteilung, Klybeckstrasse
141, 4057 Basel (CH).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT,
RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

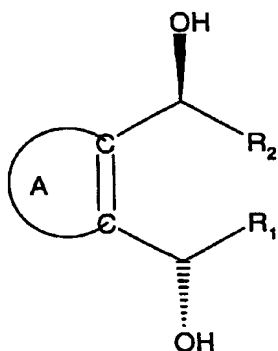
Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

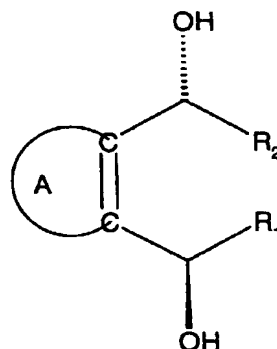
(88) Date of publication of the international search report:
23 December 2004

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: CHIRAL DIOLS, THEIR MANUFACTURE AND LIGANDS AND CATALYSTS DERIVED THEREFROM



(IVA)



(IVB)

(57) Abstract: The present invention relates to a method for the preparation of C₂-symmetric 1,4-diols of the formula IVA or IVB, wherein ring A, R₁ and R₂ have the meanings given in the specification, that makes use of the metallation of pure enantiomers of α-(aryl or heteroaryl)-α-substituted alkanol compounds or the use of said alkanol compounds in the preparation of said mmetric 1,4-diols; novel C₂-symmetric 1,4-diols in enantiomerically pure form; and methods of use or their use in the synthesis of chiral ligands which find use to produce catalysts for a variety of asymmetric transformations such as hydrogenations.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/10568

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C29/40 C07C29/36 C07C29/38 C07F9/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KRAUS, GEORGE A. ET AL: "Direct Total Syntheses of Frenolicin B and Kalafungin via Highly Regioselective Diels-Alder Reactions" JOURNAL OF ORGANIC CHEMISTRY (1995), 60(5), 1154-9, 1995, XP002235588 *scheme 1, scheme 2 and experimental section, compound 5*	1, 3, 4
X	KRAUS, GEORGE A. ET AL: "Regiocontrol by remote substituents. An enantioselective total synthesis of frenolicin B via a highly regioselective Diels-Alder reaction" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY (1993), 115(13), 5859-60, 1993, XP002235589 *scheme 1*	1, 3, 4

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the International search

12 August 2004

Date of mailing of the International search report

05. 11. 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Lorenzo Varela, M.J.

INTERNATIONAL SEARCH REPORT

Intern. Application No
PCT/EP 03/10568

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KAISER, FLORIAN ET AL: "Studies toward the Total Synthesis of Mumbaistatin, a Highly Potent Glucose-6-phosphate Translocase Inhibitor. Synthesis of a Mumbaistatin Analogue" JOURNAL OF ORGANIC CHEMISTRY (2002), 67(26), 9248-9256, 2002, XP002235590 *page 9250, scheme 2 and right column, first paragraph*	1,3,4
X	SEMMEHACK, M. F. ET AL: "Direct synthesis of pyran-lactones related to naphthoquinone antibiotics" TETRAHEDRON LETTERS (1984), 25(30), 3171-4, 1984, XP009008210 *page 3171, compound 2; page 3172, compounds 7A, 7B*	1,3,4
X	SAULNIER, MARK G. ET AL: "4-(Phenylsulfonyl)-4H-furo[3,4-b]indole - a stable synthetic analog of indole-2,3-quinodimethane" TETRAHEDRON LETTERS (1983), 24(49), 5435-8, 1983, XP009008233 *page 5437, specially scheme III and compound 12*	1,3,4
X	KRAUS, GEORGE A. ET AL: "Regiocontrol by remote substituents. The total synthesis of racemic hongconin" SYNLETT (1993), (7), 525-6, 1993, XP001146731 *scheme 1, the production of compounds 4 and 5*	1,3,4
X	MEYER, NORBERT ET AL: "Direct ortho-metalation of benzyl alcohols. A novel preparation of ortho-substituted benzyl alcohols" CHEMISCHE BERICHTE (1980), 113(4), 1304-19, 1980, XP009008271 *page 1306-1308; page 1309, first paragraph and table 4; page 1314, last paragraph; page 1980, lines 20-45 and page 1316*	1-4
X	BUTZ, RALF H. J. ET AL: "Synthesis and Chemistry of 4,5-Dimagnesiumimidazole Dianions" JOURNAL OF ORGANIC CHEMISTRY (2002), 67(8), 2699-2701, 2002, XP002235591 *table 1, entries 1, 3 and 6-8; experimental section, compounds 7, 9, 12, 13 and 14*	4
	-/-	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KLEIJN, H. ET AL: "Enantioselective dialkylation of 1,2-phthalicdicarboxaldehyde" TETRAHEDRON LETTERS (2001), 42(23), 3933-3937, 2001, XP004249125 *scheme 3 and table 2, compounds 8 and 9; scheme 4 and table 3, compounds 10-12*	4
X	SKABARA, PETER J. ET AL: "Novel Terthiophene and Bis(thienyl)furan Derivatives as Precursors to Highly Electroactive Polymers" JOURNAL OF ORGANIC CHEMISTRY (1999), 64(17), 6418-6424, 1999, XP002235593 *scheme 2, compound 14 and page 6420, left column, third paragraph*	4
X	RAMACHANDRAN, P. VEERARAGHAVAN ET AL: "Efficient synthesis of enantiomerically pure C2-symmetric diols via the allylboration of appropriate dialdehydes" TETRAHEDRON LETTERS (1997), 38(14), 2417-2420, 1997, XP004056721 *pages 2418 and 2419, compound 4a*	4
X	DERON, AGNIESZKA ET AL: "NMR studies of the bishydroxy bisphosphonate synthesis from o-phthalic aldehyde and diethyl phosphite" HETEROATOM CHEMISTRY (2002), 13(2), 157-164, 2002, XP009008214 *page 159, compounds 4a and 4b; table 1, compound 4a and page 163, second and third paragraphs*	4
X	FUJII, SHOZO ET AL: "Thermal condensation of imidazole with trifluoroacetaldehyde" JOURNAL OF FLUORINE CHEMISTRY (1986), 30(4), 415-28, 1986, XP009008258 *page 417, the table, product IVa and the first paragraph; page 418, compound IVa; page 423, last paragraph and page 424, first paragraph*	4
X	TIKK, ISTVAN ET AL: "(Hydroxyimino)isoquinolin-3(2H)-ones. Part 7. Rearrangement of 4-(hydroxyimino)-1,4-dihydroisoquinolin-3(2H)-ones under Wolff-Semmler type reaction conditions" JOURNAL OF CHEMICAL RESEARCH, SYNOPSES (1987), (4), 95, 1987, XP009008273 *last paragraph and scheme 1, compounds 9a and 9b*	4

-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 03/10568

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002235939 retrieved from BEILSTEIN Database accession no. brn 1284577 abstract & RASHID; READ: J. CHEM. SOC. C, 1969, pages 2053-2058, -----	4
X	JOUSSEAUME, BERNARD ET AL: "'4 + 2! Cycloadditions of acetylenic organotins: synthetic applications of polyfunctional cyclic vinyltins" TETRAHEDRON (1989), 45(4), 1145-54, 1989, XP001146729 *page 1151, especially, table III; page 1153, last paragraph and page 1154, first paragraph* -----	4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/10568

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 4(part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 - 4

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 4(part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which part of claim 4 may be said to define subject-matter for which protection might legitimately be sought. For these reasons, a meaningful search over the whole breadth of the claim is impossible.

Only some of the documents found are cited in the search report.

In view of the large number of compounds novelty destroying for the subject-matter of claim 4, the claim should be deleted.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.